REMARKS

Claims 39, 56, 57, 60-62 and 66-77 are pending. Claims 1-38, 45-55, 58, 59 and 63-65 have been canceled without prejudice. Support for the amendments is found on pages 11, 24, 27 and Example 2 among other locations throughout the specification. Reconsideration of the rejection is respectfully requested.

From the Official communications of September 4, 2003 and December 12, 2003, it is clear that the responses filed June 18, 2003 and September 12, 2003 were not entered and thus the amendment filed herewith reflects the total response intended.

The specification was objected to because the title was allegedly not descriptive. The title has been amended to more closely resemble the present claims.

The examiner has noted a blank on page 39 of the specification. Page 39 has been amended to complete the serial number and to update the status of those applications as issued U.S. Patents.

Claims 39, 56-57 and 60-62 were rejected under 35 USC 112, second paragraph as being indefinite in certain recitations. As for "abnormal amount", this has been changed to a different amount compared to the control to avoid any confusion. Antecedent basis for "said disease state"; "the individual" and "said markers" was present though perhaps in the singular vs. plural form. The claims have been amended to avoid single/plural confusion.

As for the alleged indefiniteness of "the levels of each protein in said proteome" as a protein can have only one level, this is disagreed with because the term "proteome" is a collection of many individual proteins as defined in the specification on page 11. While each individual protein has only one level, the proteome has many "levels", one for "each protein". As for how the levels can be compared, claim 60 was amended to state that they are compared to the levels of the corresponding protein in the control sample. This was implied before and by explicitly stating so should add to clarity. Therefore, the claim language is definite.

Claims 39, 56 and 60-61 were rejected under 35 USC 102(b) as being anticipated by Pleibner et al. The previous claims differed and the present claims differ in several aspects.

All of the claims recite measuring the proteins from a body fluid. Pleibner et al measures proteins from a chunk of heart tissue, which is not a body fluid. This difference is not trivial as stated in the specification on page 11, second paragraph. Body fluids are not the tissue specifically affected by the disease but rather may or may not be indirectly affected. Changes in heart muscle proteins noted by Pleibner et al may not be reflected in body fluids and there is no reason to believe that any proteins, much less the same proteins would be perturbed in the blood from the Pleibner et al teaching.

All claims recite determining a plurality of protein markers/targets whereas Pleibner et al state that they found only one protein, which differed markedly with a p value of <0.05. (Abstract, line 17-19; page 4047, table 2, etc.). One protein is not a plurality of proteins. Furthermore, the newly added claims recite that the differences must have a statistical significance of $p < 0.01$ and $p < 0.001$. Pleibner et al table 2 is entitled "The four most different protein spots between hypertensive and control group..." and shows only one with a significance within the broadest range claimed and none within the narrowest range claimed. This is all the more significant because the present invention is measuring proteins in indirectly affected body fluids rather than directly affected tissues.

All of the claims recite that the subject providing the body fluid has the various disease states. In Pleibner et al, rats are artificially given high blood pressure by clamping a renal artery. This is an artificial system, which essentially never occurs in nature and thus induces an artificial protein response rather than the abnormal protein abundances resulting from a disease state. Accordingly, Pleibner et al neither teach nor would be expected to achieve the same results as that of the present invention. Certainly, Pleibner et al lack any teaching of using samples from individuals with other diseases.

Claim 39 last paragraph recites determining proteins markers involved in a metabolic pathway of the disease. Pleibner et al provides no evidence any protein found correlates to any metabolic pathway. Pleibner et al does not even analyze the protein spots to identify the protein. While the rejection and the reference state that the spot is located near where the creatine kinase M-chain should be located, Pleibner et al never determined what protein this spot is and did not, actually state what protein(s) is present in the spot. As one can see, the gels have hundreds (or thousands) of spots and a number of other spots

are located in the same general area as where the creatine kinase M-chain should be. Without identifying the proteins altered, one cannot make any conclusions about what it is, whether it is involved in any metabolic pathway, have anything to do with a disease or simply be a random artifact of the experiment.

It should also be noted that all of the newly added claims recite features also not found in Pleibner et al.

Claims 57-62 were rejected under 35 USC 103 as being unpatentable over Pleibner et al in view of Chambers et al. Deficiencies in Pleibner et al are discussed above. Chambers adds little other than a review of potential uses for Proteomics. The combination provides no more than an invitation to experiment widely in the field of Proteomics and a hope for results. Applicants agree that the field of Proteomics may yield valuable information and applicants and their competitors already have several other patents in this field. However, none of this suggests that the entire field is closed to new inventions. The present claims are not directed to a general suggestion to do proteomic experiments, but rather involve a novel protocol used for successfully finding indirect markers and targets in certain specific disease states.

Chambers et al has many of the same deficiencies such as using solid tissue rather than body fluids; see page 280, column 2, lines 20-21; Figure 1, line 1; page 283, second column. Much less for blood derived fluids (claims 76-77) The applications to many diseases such as cancer, neuropathology, cardiovascular disease and microbiology all involve tissues and cells, not body fluids.

Furthermore, neither reference suggests that this approach may be useful for finding targets/markers for obesity, osteoporosis, diabetes or osteoarthritis, (claims 70-71) much less actually show successful results from samples other than those directly affected by any disease processes. Chambers et al lacks any teaching of strongly altered abundances along the lines of claims 66-69.

Still further neither reference alone or in combination suggest using identical twins or the advantages thereof (claims 57, 62).

While some of the sample preparation steps in Chambers et al may be considered a fractionation, neither reference teach specifically removing a predetermined protein

without affecting the remainder (claims 72-75). This is particularly important with plasma or serum samples where the four proteins removed by immunosubtractive chromatography in the specification examples constitute the vast majority of protein molecules present, thereby providing for easier identification of less abundant proteins.

With so many claimed differences, which are neither taught nor suggested by either reference, it would be unobvious to consider any possible combination as rendering the claimed invention patentable.

Claims 40-44 remain technically withdrawn. However, as these claims are dependant upon elected claims and have similar issues regarding patentability, they are available for easy rejoinder upon allowance of the other pending claims.

CONCLUSIONS

In view of the amendments and comments above, the rejections have been overcome. Reconsideration, withdrawal of the rejections and early indication of allowance are respectfully requested.

The commissioner hereby is authorized to charge payment of any fees under 37 CFR § 1.17, which may become due in connection with the instant application or credit any overpayment to Deposit Account No.500933.

Respectfully submitted,

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